

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
13 January 2005 (13.01.2005)

PCT

(10) International Publication Number
WO 2005/003367 A3

(51) International Patent Classification⁷: **C12P 35/04**,
C07D 501/00, C12N 9/84, 11/04

(21) International Application Number:
PCT/EP2004/007291

(22) International Filing Date: 1 July 2004 (01.07.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
03077102.6 3 July 2003 (03.07.2003) EP
03104445.6 28 November 2003 (28.11.2003) EP

(71) Applicant (for all designated States except US): DSM
IP Assets B.V. [NL/NL]; Het Overloon 1, NL-6411 TE
Heerlen (NL).

(72) Inventors; and

(75) Inventors/Applicants (for US only): LENHARDT, Carlos, Enrique [ES/ES]; Rambla de la Fontcalda 30, E-08328 Alella (ES). MOODY, Harold, Monro [NL/NL]; Akelei 9, NL-6271 ED Gulpen (NL). DOOREN, VAN, Theodorus, Johannes, Godfried, Maria [NL/NL]; Henri Tjissenstraat 56, NL-6042 BZ Roermond (NL). HEEMSKERK, Dennis [NL/NL]; Eindstraat 30, NL-6451 AD Schinveld (NL). HOGENBOOM, Anja Gerarda Margaretha [NL/NL]; Vlaskuileweg 45, NL-6105 CN Maria Hoop (NL).

(74) Agents: ELKENBRACHT, Johan, Christiaan et al.; DSM Intellectual Property, Delft Office (600-0240), P.O. Box 1, NL-2600 MA DELFT (NL).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
26 May 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PREPARATION OF CEPHRADINE

(57) Abstract: The present invention describes a process for preparing cephradine, said process comprising reacting 7-aminodesacetoxy cephalosporanic acid (7-ADCA) with D-dihydrophenylglycine in activated form (DHa) in the presence of an enzyme in a reaction mixture to form cephradine, resulting in a conversion of 7-ADCA into cephradine of at least 70 %, wherein the concentration D-dihydrophenylglycine (DH) in the reaction mixture is below 2 wt.%, wherein the conversion of 7-ADCA into cephradine is $n_{\text{CEF}}/n_{7\text{-ADCA}} \times 100\%$, wherein n_{CEF} =quantity of cephradine formed (in mole); and $n_{7\text{-ADCA}}$ =total quantity of 7-ADCA added to reaction mixture (in mole). The invention also describes a process for the preparation of cephradine hydrate characterised in that the process comprises: - reacting 7-amino acid desacetoxy cephalosporanic acid (7-ADCA) with DHa in the presence of an enzyme in a reaction mixture to form cephradine; - preparing an aqueous solution comprising at least part of the cephradine; and crystallising the cephradine from said aqueous solution. The invention further describes cephradine hydrate obtainable by a process according to invention. The invention also describes cephradine hydrate with an absorbance at 450 nm of below 0.050.